

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

COMMITTEE:

Dr. Cattell, Chm.
Dr. Bing
Dr. Jacobson

633 THIRD AVENUE
NEW YORK, N. Y. 10017

Activated: 10/15/66

cf. #398

Activated: 10/15/63

Renewed: 10/15/64

Renewed: 10/15/65

Application For Renewal of Research GrantFirst ☒ Second ☐

Date: July 31, 1967

1. Name of Investigator(s): (include title and degrees) Kenneth M. Moser, M.D.
Associate Professor of Medicine
2. Institution & Address: Georgetown University Medical School, Washington, D. C. 20007
3. Short Title of Project: Smoker-Non-Smoker Differences in Activation of Fibrinolytic-Coagulation Systems.
4. Proposed Renewal Starting Date: (Anniversary or other) 1 November, 1967.
5. Discuss any Important Changes or Additions to Objectives or Specific Aims: No major changes have occurred in objectives or specific aims from those stated in the 1966 application. The goal is still to define smoker-non-smoker differences in coagulation-fibrinolytic behavior which might bear upon the statistic relationship between heart disease (especially coronary thrombosis) and cigarette smoking.
6. Give a Brief Statement of your Working Hypothesis if altered or modified: The basic hypothesis remains unaltered; namely, that smoking may enhance thromboatherogenesis via the coagulation-fibrinolytic system.

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7. Changes or Additions to Experimental Design and Procedures: (Attach Separate Pages) At present, there have been no major changes in experimental design. However, if current trends in data are substantiated three additions to the protocol may be instituted: 1) study of the changes in "platelet adhesiveness" associated with smoking (in smokers) or hyperventilation (non-smokers); 2) limited studies of fibrinogen turnover rates in age-sex matched smokers and non-smokers; 3) addition of an exercise test to the nicotinic acid stimulus; i.e., to determine whether exercise produces the same type of smoker-non smoker differences as does nicotinic acid.

The rationale for these potential additions lies in the data appended (Tables I-3). We have recently subjected a considerable amount of our data in this study to computer statistical analysis (mean, standard deviation, standard error, correlation and "t" tests). This analysis has revealed several instructive smoker-non-smoker differences. In baseline-only studies (Table I) smokers have a statistically significant ($P < .05$) higher level of plasminogen. While other differences exist, they are not statistically significant. However, in this analysis there is a significant positive correlation between age and fibrinogen concentration in non-smokers - not in smokers. Thus smokers do not appear to have the expected age-related rise in fibrinogen, although the mean fibrinogen is higher in smokers. (Continued - pages 2-A thru 2-E)

8. Additional Requirements: We currently have no major additional requirements.

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9. Changes in Personnel with Biographical Sketches of new Personnel (append) Dr. Paul G. Harsanyi joined our research staff this year. (see attached bibliographic sketch, page 2-F)

10. Publications or Papers in Press resulting from the Project or closely related work The data presented in Tables I-3 is currently being prepared for publication.

7. Changes or Additions, cont.

On the acute smoking (or hyperventilation) studies, other interesting data appear (Table 2). Again, there is a positive age-fibrinogen correlation in non-smokers only, with fibrinogen levels again higher (but not quite significant at $P < .05$) in smokers. The plasminogen levels are again significantly higher in the smokers. In both groups, there is a highly significant rise in plasminogen ($P < .001$) with smoking (or hyperventilation). Partial thromboplastin time behavior is also interesting. In this study, baseline PTT was longer in smokers (not significantly) but fell with smoking and after smoking. In non-smokers, PTT increased slightly with and following hyperventilation.

In the nicotinic acid study (Table 3) to date, instructive data have been generated. The most striking is the fact that nicotinic acid provokes a much greater (and apparently more sustained) enhancement of activator activity in the non-smokers than in the smokers. Significant differences (as measured by both ELT and A-P plates) exist between smokers and non-smokers at all intervals. Thus, the non-smoker seems to release activator more readily than the smoker. If this is true under all circumstances, it would suggest thrombolysis may be impaired in smokers in terms of its response to a given stress.

As the data are extended, further computer analyses will be carried out. (A program has been developed for this specific purpose). Analysis of smoker-non-smoker differences between different age and sex-matched groups are contemplated. These may reveal differences obscured by combining all data, as has been done in the analysis reported in Tables 1-3.

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	<u>Smokers (60)</u>	<u>Non-Smokers (50)</u>
Age	40.1 \pm 14.8	39.7 \pm 21.0
Pack-Years	18.0 \pm 15.4	0
Pro. T. (Sec)	17.9 \pm 3.1	17.0 \pm 2.1
P.T.T. (Sec)	89.3 \pm 30.7	81.8 \pm 32.6
ELT (Min)	234.0 \pm 74.0	238.0 \pm 72.0
Fibrinogen (mgm%)	451.0 \pm 147.0	409.0 \pm 145.0
A-P (mm ²)	192.0 \pm 121.0	178.0 \pm 129.0
P'gen (mm ²)	329.0 \pm 70.0	297.0 \pm 94.0
C. P'gen (CRU)	5.6 \pm 4.5	3.7 \pm 3.3

Table One: Smokers versus non-smokers. Fasting morning values.

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	<u>Smokers (50)</u>					
	<u>Baseline</u>		<u>Smoking</u>		<u>Post-Smoking (60')</u>	
Age	41.0	± 15.5	--		--	
Pack-Years	19.8	± 15.6	--		--	
P. T.	17.2	± 2.8	17.2	± 2.8	17.2	± 3.0
P.T.T.	96.3	± 38.1	88.8	± 33.8	85.9	± 32.3
ELT	241.0	± 76.0	229.0	± 75.0	242.0	± 72.0
Fibrinogen	451.0	± 156.0	451.0	± 151.0	443.0	± 148.0
A-P	196.0	± 126.0	206.0	± 123.0	191.0	± 117.0
P'gen	307.0	± 73.0	314.0	± 81.0	307.0	± 72.0
C. P'gen	5.5	± 5.0	13.4	± 5.4	7.5	± 6.0

	<u>Non-Smokers (40)</u>					
	<u>Baseline</u>		<u>Smoking</u>		<u>Post-Smoking (60')</u>	
Age	41.5	± 21.2	--		--	
Pack-Years	0		--		--	
P. T.	16.6	± 2.1	17.0	± 2.4	16.9	± 2.3
P.T.T.	82.9	± 21.7	92.6	± 46.7	85.7	± 49.9
ELT	243.0	± 64.0	250.0	± 60.0	240.0	± 69.0
Fibrinogen	411.0	± 140.0	404.0	± 139.0	402.0	± 149.0
A-P	172.0	± 74.0	183.0	± 88.0	196.0	± 85.0
P'gen	288.0	± 60.0	285.0	± 69.0	290.0	± 60.0
C. P'gen	3.8	± 3.9	11.9	± 3.4	4.6	± 3.6

Table Two: Smokers and non-smokers studied before, at completion and 60 minutes after completion of a 30 minute smoking or mild hyperventilation period.

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	<u>Smokers</u>									
	0		10		20		40		60	
Age	37.8	± 12.8	--		--		--		--	
Pack-Years	16.3	± 9.8	--		--		--		--	
P. T.	16.0	± 1.9	16.4	± 2.4	16.4	± 2.2	16.3	± 1.8	16.1	± 1.8
P.T.T.	90.3	± 35.7	97.8	± 42.7	102.0	± 45.0	98.9	± 44.0	86.1	± 55.9
ELT	263.0	± 60.0	151.0	± 112.0	147.0	± 111.0	178.0	± 96.0	199.0	± 90.0
Fibrinogen	419.0	± 126.0	408.0	± 156.0	272.0	± 77.0	419.0	± 138.0	439.0	± 145.0
A-P	135.0	± 142.0	345.0	± 277.0	354.0	± 279.0	271.0	± 220.0	233.0	± 180.0
P'gen	262.0	± 79.0	266.0	± 77.0	265.0	± 73.0	274.0	± 61.0	275.0	± 75.0
C. P'gen	3.8	± 2.4	4.4	± 2.6	4.4	± 2.8	4.2	± 6.6	3.9	± 2.2

Table Three: Smokers (38) and non-smokers (30) studied before and at 10, 20, 40, and 60 minutes after 100 mgm
(A) nicotinic acid given intravenously.

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Non-Smokers

	0	10	20	40	60
Age	34.9 ± 12.8	---	---	---	---
Pack-Years	0	---	---	---	---
P. T.	16.4 ± 2.0	16.4 ± 2.3	16.2 ± 2.2	16.3 ± 2.2	16.6 ± 2.3
P.T.T.	87.6 ± 32.9	82.9 ± 31.6	87.0 ± 37.8	87.5 ± 39.0	85.2 ± 46.8
ELT	223.0 ± 73.0	74.0 ± 85.0	124.0 ± 120.0	102.0 ± 94.0	143.0 ± 91.0
Fibrinogen	355.0 ± 126.0	274.0 ± 159.0	316.0 ± 98.0	314.0 ± 153.0	360.0 ± 130.0
A-P	167.0 ± 109.0	508.0 ± 288.0	---	---	---
P'gen	280.0 ± 83.0	264.0 ± 78.0	---	265.0 ± 73.0	266.0 ± 71.0
C. P'gen	3.3 ± 1.9	4.2 ± 2.6	3.3 ± 2.3	3.6 ± 2.0	3.3 ± 1.9

Table Three: Smokers (38) and non-smokers (30) studied before and at 10, 20, 40, and 60 minutes after 100 mgm
(B) nicotinic acid given intravenously.

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2-F

Page 2, Item 9: Personnel with Biographical Sketches: Dr. Paul G. Harsanyi.

Date of birth: R R
Place of birth: Budapest, Hungary
Marital status: R R
M.D.: University of Budapest, 1962.
Internship: University of Budapest Medical Center, 1962-62.
Residency: University of Pecs Medical Center, 1963-66.
Visiting Research
Scientist: University of Vienna Medical School, 1966.
Research Associate:
Georgetown University Medical School, 1966 to present.

(NOTE: Dr. Harsanyi, who joined our Program in 1966, has made a considerable contribution to our research efforts. His departure from Hungary interrupted a promising research career there. We are delighted he has been able to resume it with us.)

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11. Budget (for coming year)

A. Salaries (Personnel by names or category)

Professional

Kenneth M. Moser, M. D.

George C. Hajjar, M. D.

Paul G. Harsanyi, M. D.

Technical

Charles Brunswick, B.S.

Dorothy Brown

Johnnie Burbank

Fringe Benefits (7.12%)

B. Consumable Supplies (list by categories)

Reagents, solutions

Glassware, needles, miscellaneous

C. Other Expenses (itemize)

Equipment maintenance and repair

Preparation of slides, graphs

Data analysis (computer time)

Payments to volunteers

D. Permanent Equipment (itemize)

Double Vortex Mixer

Hand Calculator

E. Overhead (15% of A + B + C)

% time

Amount

15

50

50

100

100

50

Sub-Total

748.00 = 11,248.00

0.00

500.00

600.00

Sub-Total

1,100.00

300.00

200.00

300.00

400.00

Sub-Total

1,200.00

200.00

200.00

400.00

2,032.00

Total

15,980.00

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature

Director of Project

Signature

Business Officer of the Institution

Telephone

337-3300

Ext. 318

Telephone

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Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

Current

Title of Project
Role of Fibrinolysis in Pulmonary Embolism

Source
Bezalel and Breth Foundations

Amount
15,000/year

Duration
1967-68

Pending

Control Mechanisms of the Fibrinolytic System in Man

National Institutes of Health

25,000/year

Jan. 1, 1968
to Dec. 31, 197

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